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Imaging Islet Cell Transplants

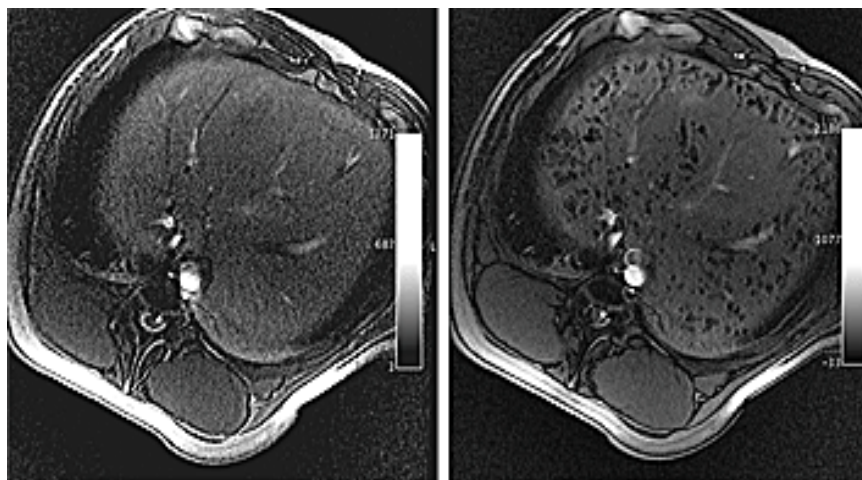


Image Title: In vivo magnetic resonance imaging of liver before (left) and 5 minutes after (right) intraportal infusion of 40,000 magnetocapsules in a swine. Magnetocapsules can be seen distributed throughout the liver as hypointense signal voids. - Brad Barnett

For patients with type 1 (juvenile) diabetes, a transplant of insulin-producing cells is a possible alternative to daily insulin injections to keep blood sugar under control. As with any transplant, however, the still-experimental technique carries the risk of rejection by the patient's immune system, meaning patients must take powerful immunosuppressive drugs. A new delivery vehicle for the transplanted cells may help overcome this obstacle, while also allowing clinicians to track the cells once they are inside the body.

The new device, called a magnetocapsule, was developed by Brad P. Barnett, a Howard Hughes Medical Institute medical student fellow in the laboratory of Aravind Arepally and Jeff W.M. Bulte at the Johns Hopkins University School of Medicine. The capsule protects the delicate pancreatic islet cells inside from attack by the host's immune system, and can be visualized with magnetic resonance (MR) imaging during and after the transplant. Visually tracking the transplanted cells could help reveal why some islet cell transplants are successful while others fail, the researchers said.

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- **Brad P. Barnett**

Barnett and a Johns Hopkins research team led by Arepally and Bulte published results of a proof-of-concept study of the magnetocapsule in an advanced online publication of *Nature Medicine* on July 29, 2007.

Researchers have found that islet cells can thrive and produce insulin in the liver - a more accessible site for a transplant than the pancreas. But once the cells are infused into the portal vein leading to the liver, there's no way to know their precise destination, which scientists suspect may influence their function.

"This is the first time we've had a tool to address the question of exactly where transplanted islet cells lodge in the liver," said Barnett. "Right now, islet cell transplantation is a black box, because we have no idea where the cells end up. Delivering islets in magnetocapsules allows us to use magnetic resonance imaging to make the transplant procedure safer and to monitor the location and extent of liver engraftment."

This is not the first time researchers have encapsulated islet cells to protect them from the body's immune system. In fact, the current research builds on microencapsulation technology originally developed in 1980. "Individual islets are surrounded with thin membranes that are permeable to insulin and nutrients, but not to antibodies," Barnett explained. "It's a common method used to isolate islets from native antibodies and avoid an immune response. The difference with our microcapsule is it incorporates an FDA-approved iron oxide formulation called Feridex® to allow for MR contrast imaging."

To create the magnetocapsules, Barnett added Feridex -- currently used for MR imaging of liver lesions -- to a membrane surrounding a cluster of 2,000 islet cells. If the capsule ruptured, the MR signal faded, which Barnett said makes it possible to monitor magnetocapsules in the liver for signs of damage.

The researchers found that the magnetocapsule had the same permeability as a traditional microcapsule, and that the islet cells inside survived just as well. They also found no significant difference in the islet cells' ability to secrete

insulin in response to high glucose levels.

To test how well they functioned inside a living animal, the researchers transplanted 6,000 magnetocapsules containing insulin-producing mouse cells into 15 mice with drug-induced diabetes. Shortly after the cell transplants, the level of glucose in the blood of all 15 mice returned to normal. Insulin levels in the mice also increased significantly during the eight-week study. In contrast, nine of the 15 diabetic mice that did not receive cell transplants died, and the others had abnormally high blood sugar levels.

Barnett and his research colleagues then infused 40,000 magnetocapsules containing human pancreatic islet cells into the portal vein of an adult pig. They used MR imaging to position the catheter and watch as the capsules spread through the pig's liver. Three weeks later, the researchers confirmed that the transplanted islets were still in place and producing human insulin.

According to Barnett, one of the most significant findings from the study is that the magnetocapsules prevented the pig's immune system antibodies from destroying the human islet cells. Pigs produce insulin that is almost identical to that made by humans, Barnett noted, and this opens the possibility of using pancreatic islet cells from pigs as an alternative source for transplants. With current technology, transplants are limited to a small number of islet cells harvested from human cadavers.

Johns Hopkins University has licensed the new technology to the Gaithersburg, Maryland company Surgi-Vision, Inc., and hopes to begin clinical trials evaluating the magnetocapsules' effectiveness in treating patients in the near future.

In addition to pancreatic islet cell transplants, scientists at Johns Hopkins University are developing other devices capable of delivering specialized cells, hormones, or drugs to precise locations in the body when and where they are needed. "You can make the capsules from different materials and put different types of cells and factors into the capsules," said Arepally. "Labeling them with different contrast agents makes it possible to use different imaging modalities, like MRI, PET or CT scans, with different cells."